REMARKS

I. Status of Claims:

Claims 1-10, 17-24, and 29-46 remain pending in this case. Claims 1-10, 22-24, and 32-34 are under examination in this application, claims 11-16 and 25-28 having been previously cancelled and claims 17-21, 29-31, and 35-46 withdrawn from consideration. Claim 4 is amended to correct a typographical error. No new matter has been added.

Applicants ask that the withdrawn process claims (*i.e.*, claims 21, 29-31, and 35-46) be rejoined once the composition claims are deemed allowable.

II. Rejections under 35 U.S.C. § 103(a):

Claims 1-10, 22-24, and 32-34 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Ozaki et al., *Blood* 102:933a (2003) ("Ozaki") in view of Beresford et al., *Int. J. Cancer* 81:911-917 (1999) ("Beresford").

According to the Office action at pages 5-6, Ozaki teaches a 2D7 antibody, the same antibody disclosed in the specification as being used to produce a sc(Fv)2 antibody. The Office action acknowledges at page 6 that Ozaki does not teach a sc(Fv)2 antibody, but alleges that Beresford makes up for this deficiency by teaching production of sc(Fv)2 antibodies that, according to the Office action, "have higher tumor uptake and retention than scFv (table 1 and page 915 bottom of 2nd column to page 916)." Applicants respectfully traverse this rejection on multiple grounds, as discussed below.

Focusing initially on the disclosure of Ozaki, Applicants again (as in the prior Reply filed January 13, 2010) point out that one of ordinary skill in the art would not have been able to produce an anti-HLA sc(Fv)2 based on the 2D7 antibody and (scFv)2 mentioned in Ozaki, because this abstract merely mentioned the 2D7 antibody and (scFv)2 by name and activity, and did not in any way put them into the hands of the public, e.g., by providing the sequence of the antibody or by making samples of the 2D7 antibody or hybridoma available to the public. Without access to the sequence or samples of the antibody or hybridoma, one of ordinary skill in the art would recognize that it is essentially impossible to reproduce the 2D7 antibody or its

CDRs or variable domains, so essentially impossible to make a sc(Fv)2 based on the 2D7 CDRs or variable domains. Accordingly, without access to the sequence or samples of the antibody or hybridoma, one of skill in the art (even high skill) would not have a reasonable expectation of success in creating the claimed antibody. It cannot be "obvious" to make something that is essentially impossible to do in that it requires information or materials unavailable to the art at the time of the invention.

The Office action attempts to rebut Applicants' argument regarding Ozaki on two grounds.

First, the Office action at page 6 characterizes Applicants' argument as "directed to the operability of the prior art." According to the Office action,

> When the reference relied on expressly anticipates all of the elements of the claimed invention, the reference is presumed to be operable. Once such a reference is found, the burden is on applicant to provide facts rebutting the presumption of operability. In re Sasse, 629 F.2d 675, 207 USPQ 107 (CCPA 1980). (see MPEP 2121).[1]

The Office appears to mischaracterize Applicants' position as expressed in the prior Response and reiterated above. Applicants have not questioned whether the prior art antibody is "operable." The 2D7 antibody likely does exactly what Ozaki says it does and can be used in the manner described by Ozaki. Rather, Applicants have simply pointed out the fact that Ozaki did not put the 2D7 antibody into the hands of the public, whether by informing the public of the sequence of 2D7 (or its variable domains or CDRs) or by granting the public access to samples of the antibody or its hybridoma. This has nothing to do with "operability" (i.e., whether the antibody does what the reference says it does). Instead, it has to do with whether one of ordinary skill in the art would have been able to make the antibody as claimed—an entirely different issue.

Applicants remind the Examiner that, according to the Court of Appeals of the Federal Circuit, "[i]n order to render a claimed apparatus or method obvious, the prior art must enable one skilled in the art to make and use the apparatus or method." *Beckman Instruments v. LKB*

[1] Applicants respectfully point out that the Office has not alleged that the presently claimed invention is anticipated, so it is unclear why the Office is relying on an argument regarding anticipation.

Produkter AB, 892 F.2d 1547, 1551 (Fed. Cir. 1989); emphasis added. Applicants assert that in the present case, the prior art does not enable one skilled in the art to make the claimed antibodies. Because Ozaki provides no sequence of the 2D7 antibody and there is no suggestion in the art that samples of the antibody or cells expressing the 2D7 antibody have been made available to the public, it would have been essentially impossible for one of ordinary skill in the art to make an sc(Fv)2 antibody having the precise sets of CDRs specified in claims 8-10. Thus, although Ozaki discloses the existence of the HLA antibody named "2D7" and the (scFv)2 named "2D7DB", that information is insufficient to enable one of ordinary skill in the art to make a 2D7 sc(Fv)2 antibody, regardless of what Beresford or any other reference teaches about sc(Fv)2 in general.

The Office action addresses Applicants' position regarding availability to the public more directly by saying at page 7:

> Since the authors of the Ozaki reference are different from the instant inventive entity, it is presumed that the 2D7 antibody was available to the public.

Applicants disagree with this reasoning. Although the list of authors for Ozaki is not identical to the list of inventors of the present application, the two lists do overlap: i.e., two of the present inventors, Naoki Kimura and Masayuki Tsuchiya, are coauthors with others on the Ozaki reference. Applicants fail to see how this fact supports the Examiner's "presumption" that the 2D7 antibody was available to the public. At the time the Ozaki reference was published and at the time the present invention was made, Drs. Kimura and Tsuchiya were employed at Chugai Seiyaku Kabushiki Kaisha. See the assignments on file for the co-inventors listed on the present application, which show that all five of the co-inventors assigned their rights to Chugai Seiyaku Kabushiki Kaisha; further, the Declaration and Power of Attorney address on file for each of the co-inventors is an address at Chugai Seiyaku Kabushiki Kaisha. See also the list of institutions of the various co-authors of on the Ozaki abstract, immediately following the list of co-authors on the abstract; this list of institutions includes Chugai Pharmaceutical Co. Ltd., which is another name for Chugai Seiyaku Kabushiki Kaisha. Drs. Kimura and Tsuchiya collaborated with their

co-authors on the Ozaki abstract to conduct the research reported in the Ozaki abstract. Such a collaboration among different institutions creates no implication that the antibody was thereby made available to the public. Further, the fact that Drs. Kimura and Tsuchiya continued working on the 2D7 antibody and, with three of their colleagues at Chugai Seiyaku Kabushiki Kaisha, prepared and tested a sc(Fv)2 version of 2D7, in no way suggests that the antibody and sequence were made available to the public. The Examiner's presumption to the contrary is thus entirely unwarranted.

The second reference that is combined with Ozaki is Beresford. Regarding Beresford, the Office action at page 6 states:

> Beresford, et al. teach production of sc(Fv)2 antibodies that have higher tumor uptake and retention than scFv (table 1 and page 915 bottom of 2nd Column to page 916).
>
> It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the antibody of Ozaki, et al. to produce an sc(Fv)2 which maintained the cell death inducing, cell growth inhibiting and anti myeloma functions in view of Beresford, et al.
>
> One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the antibody of Ozaki, et al. to produce an sc(Fv)2 which maintained the cell death inducing, cell growth inhibiting and anti myeloma functions in view of Beresford, et al. because Beresford, et al. teach that sc(Fv)2 molecules had higher tumor uptake and longer retention time than scFv molecules. (emphasis added)

The above-quoted text from the Office action focuses on Beresford's comparison of an sc(Fv)2 (i.e., a divalent antibody) and an scFv (i.e., a monovalent antibody), and is apparently based on the following passage in the last paragraph on page 915 of Beresford:

> The advantage of a divalent scFv is seen most strikingly in biodistribution studies in animals bearing tumor xenografts. Uptake of radiolabeled sc(Fv)$_2$ by tumor xenografts occurred rapidly, in excess of 6% ID/g by 30 min with a maximal value of 6.8% ID/g at 4 hr (compared with 4 and 3.3% ID/g for monomeric scFv; Pavlinkova *et al*., 1999b). (emphasis added)

In this passage, Beresford compared the level of uptake of sc(Fv)2 (a divalent antibody) by tumor xenografts with the lower values reported in the literature for monomeric scFv (a monovalent antibody).[2] It is not clear to Applicants why the Office action is focused on this comparison between sc(Fv)2 and a monomeric scFv. Since Ozaki disclosed a (scFv)2 (a diabody made up of two scFv), a more pertinent comparison would be between sc(Fv)2 and (scFv)2, to see if there was any motivation in the art to substitute a sc(Fv)2 for the (scFv)2 of Ozaki. Beresford actually carried out several comparisons between sc(Fv)2 and (scFv)2 prepared from MAb CC49, showing that the sc(Fv)2 and (scFv)2 derived from MAb CC49 are highly similar to each other in both tumor uptake and retention time. Table I of Beresford provides data regarding uptake of the sc(Fv)2 and (scFv)2 into tumor and other tissues. The uptake into tumor tissue reported in Table I for sc(Fv)2 resembles that reported for (scFv)2, with uptake of sc(Fv)2 slightly higher at some time points and uptake of (scFv)2 slightly higher at other time points. For the last four time points (24 hr to 120 hr), the numbers are essentially identical for these two types of antibodies. Thus, Table I of Beresford suggests that, overall, neither sc(Fv)2 nor (scFv)2 is superior to the other with respect to uptake into tumor tissue.

Regarding clearance from the blood, Beresford again teaches that sc(Fv)2 and (scFv)2 produce essentially the same results. Both are rapidly cleared from the blood, with more than 50% clearing in less than 40 minutes (page 914, left column, last paragraph). Figure 4 of Beresford is a time plot showing identical clearance rates from the blood for both sc(Fv)2 and (scFv)2. Figure 5 of Beresford shows whole-body clearance for sc(Fv)2 and (scFv)2; again, their clearance rates are essentially identical. These results are summarized at page 916, left column, lines 8-16: "Blood and whole-body clearance data are similar for both entities, with rapid clearance in both cases, suggesting no retention in the extravascular space or in any specific organ and elimination from the body probably through the urine." To the extent that

[2] The Office action also cites Table I of Beresford in support of the allegations regarding sc(Fv)2 vs. monomeric scFv, but Applicants note that Table I says nothing about monomeric scFv. Further, Applicants can find nothing in Beresford saying that sc(Fv)2 molecules had longer retention time than scFv molecules; if the Examiner continues to maintain that Beresford's comparison of sc(Fv)2 to monomeric scFv is relevant to the rejection, she is asked to point out where she found such disclosure regarding relative retention time, and why she believes it is relevant.

Beresford has any relevance at all to Ozaki and the present claims, it is as a teaching that one of ordinary skill in the art would not expect any advantage for sc(Fv)2 over an (scFv)2 such as that taught by Ozaki. Beresford's teachings regarding monomeric scFv, the aspect focused upon by the above-quoted text from the Office action, appear to be irrelevant to the question of whether one would seek to alter the (scFv)2 of Ozaki.

Thus, neither Ozaki nor Beresford provides any motivation to substitute an sc(Fv)2 structure for the (scFv)2 structure taught by Ozaki. Applicants remind the Examiner that other evidence of record, i.e., Kortt et al. Biomol. Eng. 18:95-108 (2001) ("Kortt"), actually *taught away* from doing so. As discussed in detail at pages 9-10 of the Reply filed January 13, 2010, Kortt predicted at page 104, left column, that sc(Fv)2 would be less stable to proteases than diabodies, i.e., (scFv)2, and further states at page 106, left column, that "preclinical biodistribution studies have shown that diabodies offer significant advantages over $(scFv)_2$ [*sic*, sc(Fv)2][3] and $F(ab)_2$ for imaging and therapy and will no doubt be in clinical trials within 12-24 months." It is difficult to see how one can derive from the evidence of record any kind of motivation to substitute an sc(Fv)2 structure for the (scFv)2 structure taught by Ozaki, let alone an expectation of success. The *prima facie* case of obviousness thus fails on at least four grounds: (a) lack of motivation to make the claimed antibody; (b) lack of teachings in the art sufficient to permit one of ordinary skill without access to the 2D7 antibody to carry out the preparation of an antibody sharing CDR sequences of the 2D7 antibody; (c) given the unavailability of the 2D7 antibody and sequence thereof to the public, a lack of expectation that one could possibly be successful in producing an antibody sharing the CDR sequences of 2D7; and (d) *teachings-away* in Kortt suggesting that the claimed antibody would not be adequately stable to proteases and that diabodies are preferable. Withdrawal of the rejection as not based on a proper *prima facie* case of obviousness is therefore requested.

[3] Kortt uses the term "$(scFv)_2$" to mean a single chain antibody containing four variable domains linked by linkers, i.e., what is referred to as "sc(Fv)2" in Beresford and in the present application, and used the term "diabody" to mean two separate scFv that are noncovalently associated with each other, i.e., what is referred to as "(scFv)2 in Beresford and in the present application. See the legend to Fig. 1 of Kortt, which explains that "$(scFv)_2$" means two scFvs joined via a linker.

Even if the Office had made out a proper *prima facie* case of obviousness, it would fail because of the objective evidence of unexpected results already of record. As noted above, Beresford teaches that (scFv)2 and sc(Fv)2 prepared from MAb CC49 are cleared from the blood at the same rate, while Kortt et al. predicts that sc(Fv)2 would be more susceptible to proteases and thus less stable in the blood than diabodies ((scFv)2). In marked contrast to the teachings of both Beresford and Kortt, Applicants demonstrated in the present application that the sc(Fv)2 form of 2D7 is retained in the blood significantly longer than is the (scFv)2 form of 2D7 (half life of sc(Fv)2 was 2.30 hours; half life of (scFv)2 was 1.64 hours). See Example 7 at page 24 of the Substitute Specification, and Fig. 6. (Applicants also showed that the sc(Fv)2 antibody exhibits the cell death-inducing activity and cell growth-inhibitory activity of the (scFv)2 form of 2D7. See Examples 4 and 5 at pages 22-23.) This evidence that sc(Fv)2 is retained in the blood longer than (scFv)2 is entirely unexpected in view of Beresford and Kortt's teachings to the contrary, so is cogent, objective evidence of the nonobviousness of the invention.

For at least the foregoing reasons, Applicants respectfully request that the outstanding rejection under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

Conclusion

Applicants respectfully submit that all pending claims are in condition for allowance, and therefore request the timely issuance of a Notice of Allowability.

Applicants petition for a one-month extension of time to respond to the outstanding Office Action. Please apply any required charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 14875-0166US1.

If the Examiner has any questions regarding this application, she is invited to call the undersigned at the telephone number given below.

Respectfully submitted,

Date: July 26, 2010

/Janis K. Fraser/
Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

Customer Number 26161
Fish & Richardson P.C.
Telephone: (617) 542-5070
Facsimile: (877) 769-7945

22460567.doc